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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,068	05/04/2007	Fong Poh Lisa Ng	033946-1401	6103

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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	**PAPER NUMBER**
1648	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,068	NG ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32 and 45-48* is/are pending in the application.

4a) Of the above claim(s) *10-19,22-32 and 46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,20,21,45,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/2/06 and 3/5/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-32 and 45-48 are pending in the application.

Election/Restrictions

2. Applicant's election of Group I in the reply filed on December 10, 2009, and of the species identified on page 8 of the reply, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. As asserted by the Applicant, claims 1-11 are considered to fall within the scope of elective Group I of the restriction requirement.

4. Claims 10-19, 22-6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 10, 2009.

5. Claims 1-9, 20, 21, 45, 47, and 48 are under consideration.

Information Disclosure Statement

6. The information disclosure statements (IDS) submitted on November 2, 2006 and of March 5, 2008 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-9, 20, 21, 47, and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The first basis of rejection applies to each of the indicated claims, with claim 1 treated as representative. This claim is drawn to a method for altering the load of a hepatitis virus in a host organism through the modulation of complex formation between hnRNP K "or a functional fragment thereof with a regulatory region of the Hepatitis virus genome." However, the claims are specifically drawn to the inhibition of the complex formation in a host. Thus, particularly a mammal or a human. As such, it would be expected that the claims read on the inhibition of hnRNP K with the viral genome. It is not clear what is intended by reference to inhibition of functional fragments of the protein, as those in the art would not appear to expect the presence of such fragments, separate from a full-hnRNP K protein, to be present.

The second basis applies to claim 47. This claim is drawn to a method for the treatment of a Hepatitis infection comprising the administration of "a compound identified by a method of claim 8." Claim is also drawn to such methods, and does not describe any method for the identification of such compounds, or disclose any such compounds. It is therefore not clear what is meant by the quoted claim language.

For the purposes of this action, the claim is treated a method for the treatment of a Hepatitis infection comprising the administration of the compound administered in the method of

claim 8 (i.e. is treated as incorporating the method limitations of claim 8 and the claims from which it depends).

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-9, 20, 21, 45, 47, and 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of reducing HCV viral titer in a host organism comprising inhibiting the formation of a complex between hnRNP K and the human HBV regulatory region identified in claim 8, does not reasonably provide enablement for methods of reducing viral load or treating infection by any hepatitis virus through any modulation of hnRNP K and a regulatory region of the genome in the target hepatitis virus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the

claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

The present claims are drawn to methods for altering the load of or treating an infection by a Hepatitis virus, esp. HBV, in a host organism comprising the administration of a compound that modulates the formation of a complex between hnRNP K and a regulatory region in the viral genome.

In support of the claimed invention, it is first noted that all of the data provided by the Applicant relate to HBV. There is no demonstration of interaction between hnRNP K with any other hepadnavirus, or with other non-related hepatitis viruses such as HAV and HCV. With respect to the HCV, the only evidence of interaction presented in the art is disclosed by Hsieh et al. (J Biol Chem 273:17651-59), which reference discloses only the inhibition of hnRNP K activities through binding of the protein by the HCV Core protein. None of this reference, the present application, or other teachings found in a search of the art provided any evidence of interaction between hnRNP K with regulatory regions of any hepatitis virus other then HBV.

It is also noted that the structures, functions, and infectious pathways of the different hepatitis viruses vary one from another. There is no indication of any commonality among them other than that they each target liver structures; in particular, there is no evidence in the present application or in the art that each of the various hepatitis viruses interact with hnRNP K, much less that hnRNP K interacts with regulatory regions of the viruses in such a manner that inhibiting such an interaction would result in the inhibition of viral replication or otherwise act to reduce viral titer or effect a treatment for the viral infection.

It is further noted that the claims are drawn to reduction of the viral load through the "modulation" of the interaction between hnRNP K and the viral enhancer. With respect to the viruses other than human HBV, there is no guidance as to how (inhibition or enhancement) any such interaction (if any exists) should be modulated to achieve the desired anti-viral results. With respect to human HBV, the teachings in the application specifically indicate that inhibition of such an interaction is required to achieve the desired results. Thus, while enabling for methods in which human HBV loads are reduced through the inhibition of such interactions, the application is not enabling for the practice of the claimed invention through any modulation of the target hnRNP K interaction.

The claims are therefore rejected

11. Claims 1-9, 20, and 21, 45, 47, and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

The present claims are drawn to methods for altering the load of or treating an infection by a Hepatitis virus, esp. HBV, in a host organism comprising the administration of a compound that modulates the formation of a complex between hnRNP K and a regulatory region in the viral genome. Certain of the claims limit the compound to DNA or DNA aptamers. Claims 21 and 45. Other claims provide a general mode of operation for the compound. See e.g., claims 5 and 6. Further, the majority of the claims are drawn to methods wherein the hepatitis virus may be any hepatitis virus; with only certain claims (claims 2, 8, and 9) specify that the virus is HBV. The claims are also drawn to methods wherein the desired result is achieved in vivo (e.g. in a hepatitis virus infected human such as in claims 3, 4, 45, and 47). Thus, the claims are generally drawn to method for the altering the load of, or treating infection by, any hepatitis virus in a host organism through the administration of any compound that, either directly or indirectly, modulates the interaction of hnRNP K with regulatory regions in the hepatitis viral genome.

The claims are rejected on three grounds.

First, claims 1-9, 20, and 21, 45, 47, and 48 are rejected as lacking adequate support for the inhibition of complex formation between hnRNP K and any regulatory region of any Hepatitis virus.

In support of the claimed invention, it is first noted that all of the data provided by the Applicant relate to HBV. There is no demonstration of interaction between hnRNP K with any other hepadnavirus, or with other non-related hepatitis viruses such as HAV and HCV. With respect to the HCV, the only evidence of interaction presented in the art is disclosed by Hsieh et al. (J Biol Chem 273:17651-59), which reference discloses only the inhibition of hnRNP K activities through binding of the protein by the HCV Core protein. None of this reference, the present application, or other teachings found in a search of the art provided any evidence of interaction between hnRNP K with regulatory regions, including enhancer II regions, of any hepatitis virus other then human HBV.

Further, the application also fails to specifically identify any particular sequence or structure in such regulatory regions that could be considered to correspond to the ability to form complexes with hnRNP K. While the application identifies the enhancer II domain of human HBV as forming such a complex, the application nowhere indicates what specific characteristics of this domain are targeted by hnRNP K or enable the domain to bind hnRNP K such that those in the art may be able to correlate the presence of such sequences or structures in other hepatitis viral regulatory regions with the ability to form the target complexes.

In view of the lack of any such identification of other viruses, or other hepatitis viral genomic regulatory regions, that interact with hnRNP K, or to identify any structure or other non-functional characteristic that correlates with the ability of a hepatitis viral regulatory region

to form a complex with hnRNP K, the claims are rejected as lacking adequate descriptive support for the application of the claimed method to inhibiting such interactions with Hepatitis viruses other than human HBV.

Second, claims 1-9, 20, and 21, 47, and 48 are rejected as lacking adequate support for the inhibition of complex formation between a functional fragment of hnRNP K and a Hepatitis virus genomic regulatory region. The application indicates that hnRNP K contains several modular domains which appear to perform different functions. Page 5, paragraph [0016]. The application also indicates that it contains a plurality of domains that permit its interaction with DNA and RNA. However, the application nowhere indicates which domain(s) are actually involved with its interaction with the human HBV enhancer II region, much less what domains may interaction with regulator regions of other Hepatitis viruses. In view of the lack of any such guidance, the claims are rejected as lacking adequate descriptive support for the inhibition of complex formation between such hnRNP K functional fragments and regulatory regions of the Hepatitis viruses.

Thirdly, each of the indicated claims is also rejected as lacking adequate descriptive support for the compounds that may be administered to effect the modulation of the hnRNP K viral regulatory region complex formation.

It is noted that, while the claims are drawn to the modulation of the complex formation, claim 1 is silent as to how such modulation is performed. The specification indicates that such modulation may be direct, or indirect. Pages 7-8. As indicated in the art rejection over Rang et al.

below, compounds may perform this function although having no or little interaction with hnRNP K or its gene. Thus, the claims read on any means for modulating the interaction between hnRNP K and a hepatitis viral regulatory region, regardless of the actual means by which such modulation occurs.

However, the specification provides only two examples of compounds that appear to be able to interfere with complex formation, each of which inhibits the initial production of hnRNP K. See, pages 30-32. There is no specific identification of a region of hnRNP K that may be targeted, no identification of viral regulatory regions (other than the enhancer II region of human HBV) that may be targeted, and no identification of any compound capable of directly interfering with binding between the regulatory region and hnRNP K.

Claims 5 and 6 provide additional functional description of compounds that may be used, but both the claims and the application fail to provide any correlating structure or non-functional feature that would correlate with even these functional requirements.

Claims 21 and 45 specify that the compound administered is a DNA molecule, or an aptamer. However, the application provides no examples of compounds of with DNA generally or any specific DNA aptamers that achieve the desired functions. Nor does the application provide any guidance as to what structures or DNA sequences may correlate with utility in the claimed methods. It is noted that the art indicates that methods for the identification of aptamers that perform certain binding functions are known. See e.g., Ulrich et al. (Braz J Med Biol Res 34:295-300). However, the knowledge or provision of such methods fails to provide support for compounds that may be identified through their use. See e.g., University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886, at 1895. Moreover, even though the art indicates that aptamers

that target extracellular ligands may avoid problems associated with other forms of therapeutic nucleic acids (see e.g., Pestourie et al., Biochemie 87:921-30, at page 922, right column), the present application provides only one example of such a target (page 30, identifying the epidermal growth factor receptor- EGFR), and provides no examples of aptamers against this receptor. Such teachings therefore fail to provide descriptive support for the claimed methods as they fail to provide support for the compounds that may be used in the methods.

In view of the breadth of the claimed genus, the limited provision of examples and more limited provision of non-functional characteristics that correlate to the performance of the required functions, and the general uncertainty as to what molecules and compounds may eventually be identified as either targets for such compounds or as compounds that perform the required function, the claims are rejected as lacking adequate descriptive support for the claimed genus.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-4, 6-9, and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Rang et al. (JBC 277:7645-47) in light of the teachings of Zhang et al. (Cell Microbiol 10:112-121) and Bonvin et al. (Hepatol 43:1364-74)(each of which references were made of record in the restriction requirement of September 24, 2009). These claims are drawn to methods for the

treatment of a hepatitis virus infection, esp. of a human by a human Hepatitis B virus, comprising the administration of a compound that modulates the formation of a complex between hnRNP K and a regulatory region of the viral genome. The teachings of the application indicate such modulation may be through any means (i.e. indirectly or direct modulation). See e.g., page 8 (indicating that various means for modulation of hnRNP K HBV genome complexes may be used).

Rang teaches the administration of Interferon-alpha to treat HBV infections in humans. Rang, at page 7645.The reference does not disclose the mode of anti-viral activity of the compound, and makes no mention of hnRNP K or its interaction with the viral genome. However, it is noted that later teachings in the art indicate that a protein known as A3B suppresses HBV replication through inhibiting the binding of hnRNP K to the enhancer II region of HBV. See e.g., Zhang et al., Cell Microbiol 10:112-121. The art also teaches that A3B is up-regulated in hepatic cells in response to interferon-alpha. Bonvin et al., Hepatol 43:1364-74. Thus, the teachings in the later art indicate that upon stimulation with interferon-alpha, hepatic cells up-regulate A3B, which then acts as an inhibitor or hnRNP K binding to the HBV genome, thereby inhibiting viral transcription and altering the load of the virus in the patient.

In view of the A3B up-regulation by interferon-alpha in hepatic cells, the teachings of the later art indicate that the interferon-alpha administration of the Rang reference would inherently have resulted in the modulation of HBV through the mode required by the claims. The method of Rang therefore anticipates the indicated claims.

Conclusion

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is (571)272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick J. Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachariah Lucas/
Primary Examiner, Art Unit 1648